REMARKS

The undersigned thanks Examiner Yu for the courtesies extended during the interview of May 23, 2006. Prior to the interview, the undersigned faxed a copy of the proposed Amendment to the Examiner. The Examiner was well-prepared for the interview. The Interview Summary states:

> Applicant argued that amended claim 1 recites attaching an organic molecule to metallic colloid wherein the organic molecule attaches to the colloid and also has affinity for a biomolecule. Applicant argues that Siiman & Kidwell do not teach this limitation. The protein of Kidwell does not have affinity for both a metal colloid and a biomolecule.

Applicants fully agree with the Examiner that the protein of Kidwell (column 6, line 66) does not have affinity for both a metal colloid and a biomolecule. Also, the Examiner stated during the interview that Siiman fails to disclose attaching an organic molecule to metallic colloid wherein the organic molecule attaches to the colloid and also has affinity for a biomolecule. Applicants agree.

On May 24, 2006, Examiner Yu called the undersigned that she had spoken to her SPE who said that the Amendment would likely overcome the pending prior art rejection, but the Examiner still needs to undertake another prior art search.

The amendments of claims 1 and 9, and new claims are fully supported by the specification. For example, see original claims 7 and 9, paragraphs [0016], [0018], [0019] and Figures 2 and 3.

Claim 1 is directed to a method for producing a metallic colloid, comprising particles comprising a metal and an organic molecule, the method comprising: preparing a solution comprising cations of the metal and a reducing agent by dissolving the cations and the reducing agent in the solution, *subsequently* heating the solution to produce the metallic colloid, and attaching the organic molecule to the metallic colloid, *wherein the organic molecule comprises a*

moiety that has an affinity for the metallic colloid and another moiety that has an affinity for a biomolecule.

Please note that the method of claim 1 includes "attaching the organic molecule to the metallic colloid, wherein the organic molecule comprises a moiety that has an affinity for the metallic colloid and another moiety that has an affinity for a biomolecule." This limitation is *not* disclosed in any of the cited prior art references. Thus, for this reason alone, this invention is patentable over the cited prior art references.

As a result of attaching the claimed organic molecule to the metallic colloid, wherein the organic molecule comprises a moiety that has an affinity for the metallic colloid and another moiety that has an affinity for a biomolecule, Applicants were able to solve a *long-felt need* to prevent aggregation of the metallic colloid particles *without* attaching a biomolecule to the metallic colloid. The problem that existed in the prior art has been explained, for example, in column 6, lines 45-47, of Kidwell (which has been cited by the Examiner):

> The metal particles will aggregate if the biomolecule is not coated sufficiently on the surface. This aggregation takes several hours to days at room temperature.

To overcome the aggregation problem, Kidwell coats the metallic colloidal particles directly with a biomolecule *immediately* after manufacturing the metallic colloidal particles. See column 6, lines 65-68, of Kidwell. Thus, according to Kidwell's method, each time a biomolecule needs to be tested, one needs to first make the metallic colloid and immediately attach the biomolecule to the metallic colloid. In short, the metallic colloid of Kidwell suffers from a serious deficiency in that it *cannot* be stored for durations beyond several hours or days at room temperature without attaching a biomolecule to the metallic colloid. Thus, there has been a *long-felt need* to make free-standing metallic colloid that does not have a biomolecule attached to it and that can be stored and later used with a plurality of biomolecules. This *long-felt need* has been fully and satisfactorily addressed by this invention.

For example, by the embodiments of this invention, it is now possible to attach an organic molecule with a moiety that has selective affinity for only a particular biomolecule. Thus, by the screening methods developed using the metallic colloid of the embodiments of this invention, it is now possible to attach a particular biomolecule from a system such as a solution containing a plurality of biomolecules. Kidwell's and other prior art methods would not allow such selective attachment of a particular biomolecule as Kidwell's metallic colloid would bind to many different biomolecules when the metallic colloid was exposed to a plurality of biomolecules.

Also, as explained in paragraph [0018] of the specification, "[t]he methods for producing metallic colloids" as claimed "are in contrast to prior methods wherein a boiling silver nitrate solution is titrated with a sodium citrate solution." For example, Siiman, which has been cited by the Examiner, clearly relates to such a prior art method. See column 12, lines 55-67, of Siiman. In contrast to the method of Siiman, the claimed method clearly recites "*subsequently* heating the solution to produce the metallic colloid."

Applicants respectfully submit that the Examiner should not read out the limitation "subsequently" in claim 1 just as the Federal Circuit in *Lewmar Marine Inc. v. Barient Inc.* 827 F.2d 744, 3 USPQ2d 1776, *cert. denied*, 484 U.S. 1007 (Fed. Cir. 1988), explained that even the word "only" cannot be read out of a claim. "The claim limitation could possibly read on the American Eagle winch if the word 'only' did not appear in that clause. The word 'only,' however, is there and may not be read out of the claims." *Id.* Similarly, in this case, the word "subsequently" may *not* be read out of the claims.

By this invention, besides providing a solution to a *long-felt need*, Applicants have also demonstrated *unexpected results* by showing that "[t]the Raman signal is on average 50% higher than the best silver lot from the titration method" (see Figure 2). Also, as explained in paragraph [0018], the titration method of Siiman is fraught with problems, namely that "[t]his titration method can produce only one batch of silver particles with adequate Raman enhancement to

dAMP in about 10 attempts, and the other batches have low or no Raman activity at all." Paragraph [0016] further states, "However, by employing the methods of the invention, an average SERS signal enhancement of 150% is observed relative to colloids prepared from the titration method." Also, as stated in paragraph [0016], the embodiments of the claimed "method results in a 50% enhancement of SERS signals obtained from such colloids, and also results in a increase in reproducibility of 10-20% to 80-100%."

These *unexpected results* were neither known to persons of ordinary skill in this art prior to this invention nor expected. Thus, "[c]onsistent with the rule that all evidence of nonobviousness *must* be considered when assessing patentability, the PTO *must* consider comparative data in the specification in determining whether the claimed invention provides unexpected results." *In re Soni*, 54 F.2d 746, 34 USPQ2d 1684 (Fed. Cir. 1995) (emphasis added). Prior to this invention, it was *not* possible to store a metallic colloid of the prior art without attaching a biomolecule; it was *not* possible to screen a particular biomolecule from a plurality of biomolecules using the metallic colloid; and in addition the SERS signal enhancement by the metallic colloid and reproducibility of the SERS signal were poor. As a result of the claimed invention, all of these deficiencies in the metallic colloid of the prior art have been resolved.

In the event that the transmittal letter is separated from this document and the Patent and Trademark Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **070702003400**.

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Respectfully submitted,

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